

Occult *Enterobacter aerogenes* Pneumonia Diagnosed by Indium 111-Labeled Leukocyte Scan

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OCCULT INFECTION is a common clinical challenge in intensive care units but is uncommonly ascribed to pneumonia, which is usually excluded by a normal chest roentgenogram. Exceptions include *Pneumocystis carinii* pneumonia and tuberculosis,^{1,2} as well as bacterial pneumonia in neutropenic patients, all of which may present with initially clear lung parenchyma on a chest radiograph. Among the imaging techniques that have been proposed to identify the site of occult infection are computed tomography (CT), magnetic resonance imaging, and radiolabeled isotope scans using both gallium 67 and indium 111-labeled leukocytes, the latter of which has been found to be variably effective for diagnosing lung infection, such as pneumonia and abscess.

To extend the recognized spectrum of occult pulmonary infections that may be truly occult and to emphasize the value of [¹¹¹In]leukocyte scans in their detection, the following report demonstrates the use of [¹¹¹In]leukocyte scanning to localize an occult pneumonia due to *Enterobacter aerogenes* in a ventilator-dependent, non-immunocompromised patient.

Report of a Case

The patient, a 68-year-old man, was admitted to an outlying hospital with acute, severe low back pain. A CT scan of the abdomen revealed a leaking abdominal aneurysm, and the aneurysm was repaired using aortobifemoral graft placement. His postoperative course was complicated by cardiac arrest with cardiogenic pulmonary edema leading to respiratory failure, renal failure, and fever of an unknown origin. His medical history included atherosclerotic heart disease, peripheral vascular disease, type II diabetes mellitus, heavy smoking with presumed chronic obstructive pulmonary disease, and a history of histoplasmosis diagnosed by wedge resection.

On transfer to the Cleveland Clinic Hospital ten days after the operation, the patient was obtunded and required mechanical ventilation. Laboratory evaluation showed a leukocytosis— 15.3×10^9 per liter (15,300 per μ l)—and tracheobronchial secretions showed few neutrophils but a moderate growth of *E aerogenes*. The parenchyma on the chest roentgenogram was clear. Therapy with vancomycin hydrochloride and ceftazidime had been begun for fever and leukocytosis at the referring hospital but was discontinued on arrival, with cultures of blood and urine done after antibiotics were discontinued failing to grow organisms. Another CT

scan of the abdomen showed no suggestion of graft infection, and the sections through the lower chest were normal. In an effort to identify a presumed occult infection, a scan using [¹¹¹In]autologous/oxine-labeled leukocytes was done (Figure 1). It showed grade III (intensity of uptake equal to liver) uptake in the lungs at a time when the lung parenchyma on chest x-ray film from the same day was interpreted as normal (Figure 2). The [¹¹¹In]leukocyte scan was taken 24 hours after administering autologous leukocytes labeled with a dose of 500 μ Ci of [¹¹¹In]. The labeled cells were administered within two hours of procurement, and scanning was completed by a Siemens Bodyscan dual-head imager.

To pursue further the possibility of occult pulmonary infection, a bronchoscopy was done the following day with right lower lobe bronchoalveolar lavage. Analysis of the lavage fluid revealed 525 per μ l of erythrocytes and 153 per μ l of leukocytes. The differential cell count was polymorphonuclear leukocytes, 0.23; lymphocytes, 0.03; monocytes, 0.04; and alveolar macrophages, 0.69. Cultures of the lavage fluid grew 10^4 colony-forming units (CFU) per milliliter *E aerogenes* and 10^5 CFU per ml γ -*Streptococcus* species. Sensitivity analysis showed the *E aerogenes* organisms to be resistant to semisynthetic penicillins and cephalosporins but sensitive to both ciprofloxacin and the combination of trimethoprim and sulfamethoxazole. The combination drug was administered at a dose of 200 mg intravenously every eight hours (dose reduced because of renal insufficiency). Sensitivities of the *Streptococcus* species were not tested because the organism was interpreted as normal mouth flora. After three days, the patient defervesced and was weaned from mechanical ventilation over the next week as his mental

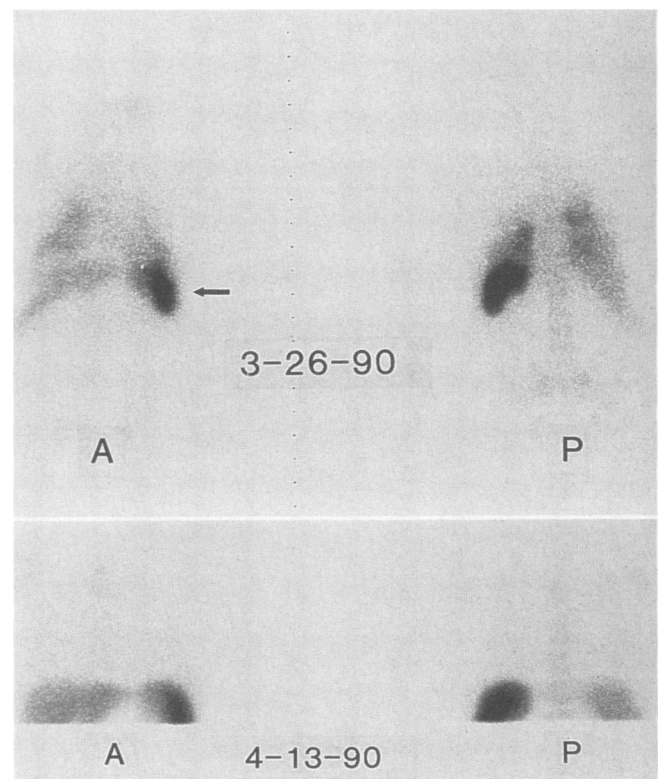


Figure 1.—Top, An indium 111-labeled leukocyte scan (24 hours) on hospital day 9 shows grade III uptake in both lung bases and in the right mid-lung zone. Splenic uptake (arrow) is grade IV. Bottom, A follow-up [¹¹¹In]leukocyte scan on day 27 shows clearing with treatment.

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ABBREVIATIONS USED IN TEXT

CFU = colony-forming units
CT = computed tomography

state improved. Chest radiographs during this time continued to show clear lung parenchyma (Figure 2), and a repeat [^{111}In]leukocyte scan 16 days after treatment showed no evidence of pneumonia (Figure 1). He was discharged to home 73 days after admission to the hospital.

Discussion

[^{111}In]Leukocyte scans are most widely used in evaluating occult infections, especially when intra-abdominal abscess or osteomyelitis is suspected.³ As reviewed in Table 1, the

uptake of radioactive indium has also been reported in a wide range of pulmonary problems.⁴⁻¹⁷

In assessing the uptake of [^{111}In], which is normally taken up by liver, spleen, and bone marrow, the degree of uptake is graded on a scale from I to IV.⁴ Grade I reflects uptake greater than that of soft tissue but less than that of rib, grade II reflects uptake equal to that of rib but less than that of liver, grade III reflects uptake equal to that of liver, and grade IV reflects uptake equal to that of the spleen.

The time course of leukocyte recruitment after the onset of lung infection is also relevant and helps explain the diagnostic performance of [^{111}In]leukocyte scans in evaluating chest infections. After inducing pneumococcal pneumonia in dogs, Dutcher and co-workers have shown that leukocyte recruitment to the lung begins within hours of exposure to pneumococci and is complete within 24 hours.¹⁸ Autoradiographs of resected lung within 24 hours of aspiration reveal labeled leukocytes filling consolidated alveoli, but more delayed administration of [^{111}In] will not produce chest uptake, presumably because leukocyte recruitment is complete by that time.⁹

[^{111}In]Leukocyte scanning has proved appealing in diagnosing extrathoracic occult infections because the reported diagnostic sensitivity ranges from 73% to 88% and the specificity ranges from 90% to 97%.^{4,18,19} The current report highlights the sensitivity of [^{111}In]leukocyte scans in diagnosing chest infection, as the radioisotope uptake was the only indicator of a true pneumonia in our patient. Three lines of evidence support this conclusion:

- Retrieval of a substantial bacterial growth ($\geq 10^4$ CFU per ml) from bronchoalveolar lavage fluid;
- Defervescence in response to antibiotic therapy (trimethoprim-sulfamethoxazole) tailored to the bronchoalveolar lavage culture results (notably *E aerogenes*); and
- Disappearance of the chest uptake of [^{111}In]leukocytes when the radioisotope scan was repeated after the patient's defervescence.

Reported experience with [^{111}In]leukocyte scans in diagnosing chest infections has been mixed, with some investigators emphasizing poor specificity (false-positive lung uptake),^{5,8} and others reporting disappointing sensitivity (false-negative [^{111}In] scans in patients with true chest infections).⁹ For example, in a recent review of 345 patients who underwent [^{111}In]leukocyte scans, 12% of patients had low-grade chest uptake without evidence of concomitant chest infection (low specificity).³ As with any diagnostic test, the diagnostic performance (sensitivity, specificity, and predictive values) varies with the criteria for a positive test. A review of available experience with indium scanning in chest infections (Table 2) suggests that the more focal the [^{111}In] uptake in the chest, the greater the predictive value of an abnormal ("positive") scan for a true chest infection. Though less well studied, the diagnostic accuracy of [^{111}In] scanning also improves as the intensity of uptake in the chest increases—for example, to grades III and IV uptake.

Other investigators have reported normal ("negative") [^{111}In]leukocyte scans in patients with known chest infections, including those with empyema, miliary tuberculosis, and pneumonia. In a series reported by Saverymuttu and colleagues, five patients with lobar pneumonia lacked chest uptake of [^{111}In] despite evidence of preserved pulmonary perfusion and extrathoracic uptake of the isotope.⁹ The putative

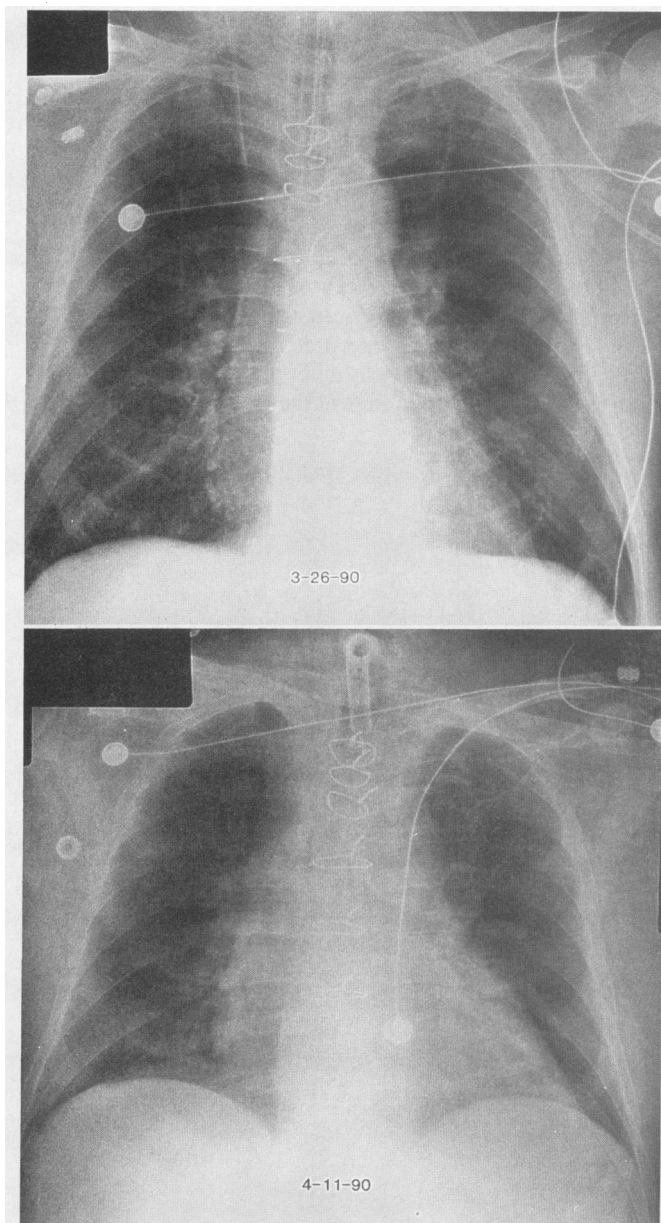


Figure 2.—**Top,** A posteroanterior chest radiograph on hospital day 9 shows clear lung parenchyma despite concurrent lung uptake of radioactive indium (Figure 1). **Bottom,** A follow-up posteroanterior chest radiograph was taken on day 25.

TABLE 1.—Pulmonary Conditions in Which Indium 111-Labeled Leukocyte Uptake Has Been Reported

Type of Pulmonary Disorder	Source
Infectious	
Pneumonia	McAfee and Samin, 1985 ⁴ ; Segall and McDougall, 1986 ⁵ ; Ascher et al, 1979 ⁶ ; Alderson et al, 1983 ⁷
Lung abscess	McAfee and Samin, 1985 ⁴ ; Cook et al, 1984 ⁸ ; Saverymuttu et al, 1985 ⁹ ; Massie and Winer-Muram, 1986 ¹⁰
Cystic fibrosis	Crass et al, 1979 ¹¹
Bronchiectasis	Currie et al, 1987 ¹²
Empyema	McAfee and Samin, 1985 ⁴ ; Segall and McDougall, 1986 ⁵ ; Cook et al, 1984 ⁸
Septic emboli	McAfee and Samin, 1985 ⁴
Infected central venous line	McAfee and Samin, 1985 ⁴
Inflammatory, noninfectious	
Adult respiratory distress syndrome	Cook et al, 1984 ⁸ ; Segall et al, 1987 ¹³
Oxygen toxicity	Alderson et al, 1983 ⁷ ; Rinaldo et al, 1988 ¹⁴
Pulmonary embolism	Segall and McDougall, 1986 ⁵
Aspiration	Cook et al, 1984 ⁸
Inactive cytomegalovirus infection	Forstrom et al, 1981 ¹⁵
Postirradiation therapy	McAfee and Samin, 1985 ⁴
Wegener's granulomatosis	McAfee and Samin, 1985 ⁴
Noninflammatory	
Congestive heart failure	McAfee and Samin, 1985 ⁴ ; Cook et al, 1984 ⁸
Atelectasis	Cook et al, 1984 ⁸
Cell clumping from dose agitation or from injection into glucose solution	Coleman and Welch, 1980 ¹⁶ ; Simerman et al, 1986 ¹⁷
Tumor or metastasis	Segall and McDougall, 1986 ⁵ ; Cook et al, 1984 ⁸
Sterile pleural effusion	Segall and McDougall, 1986 ⁵
Pulmonary hemorrhage	Segall and McDougall, 1986 ⁵
Increased interstitial markings	Segall and McDougall, 1986 ⁵
No associated thoracic disease	McAfee and Samin, 1985 ⁴ ; Segall and McDougall, 1986 ⁵ ; Cook et al, 1984 ⁸

reason for the "false-negative scans" in this series is that granulocyte recruitment to the lung that is necessary for a positive scan was already completed by the time the scan was done, hence, a falsely negative radioisotope study. Specifically, all five patients had chest symptoms of pneumonia for at least two days before the [¹¹¹In]leukocytes were administered, considerably longer than the 24-hour period in which granulocytes migrated to the chest after initial infection in dogs.⁵ In contrast to the low sensitivity in already established pneumonia, [¹¹¹In]leukocyte scans have proved sensitive in patients with bronchiectasis. Specifically, in one series, 18 patients with severe bronchiectasis and persistent sputum production were studied, of whom 16 had increased uptake of [¹¹¹In]leukocytes within 24 hours of injection.¹² Radioisotope uptake gravitated to regions of moderately severe bronchiectasis on CT scans, and ¹¹¹In radioactivity correlated roughly with the volume of 24-hour sputum production. Unlike the rapid consolidative process in lobar pneumonia, bronchiectasis is characterized by repeated cycles of infection and resultant inflammation in which granulocyte recruitment to the lung is ongoing.

As with the case reported here, several earlier reports have shown true-positive [¹¹¹In]leukocyte scans in patients

with clear chest radiographs. In a retrospective analysis of 128 patients undergoing [¹¹¹In]leukocyte scanning for suspected abdominal abscesses, 58 patients had positive scans, of whom 20 (34%) had unexpected extra-abdominal sites of uptake. Of these 20 patients, 3 had pneumonitis initially diagnosed by ¹¹¹In uptake, though the precise confirmatory method of diagnosing pneumonia in this series is unspecified. In another report, grade IV focal uptake of ¹¹¹In was reported with aspergillar pneumonia in a heart transplant patient whose pneumonia was evident only as a nodular infiltrate on chest CT scan. Autopsy-proved cytomegaloviral pneumonia was reported in a renal transplant patient in whom infiltrates developed on a chest radiograph two weeks after ¹¹¹In uptake in the chest was first evident.¹² The use of [¹¹¹In]leukocytes in the diagnosis of cytomegalovirus pneumonia was also recently reported in a renal transplant recipient with a normal chest roentgenogram.²¹

The current report extends this available experience and provides another challenge to the notion that the chest uptake of radioactive indium in a patient with a clear chest radiograph presents a false-positive scan. More systematic prospective study will be necessary before the diagnostic accuracy of [¹¹¹In]leukocyte scans for chest infection can

TABLE 2.—Diagnostic Accuracy of [¹¹¹In]Leukocyte Scans for Chest Infections in Available Series*

Study	No. Scans Positive/ Total No.	Sensi- tivity, %	Speci- ficity, %	Positive Predictive Value, %	Negative Predictive Value, %
Cook et al, 1984 ⁸	48/48 27/48†	NA NA	NA NA	33 52	NA NA
McAfee and Samin, 1985 ⁴	22/22 13/22†	NA NA	NA NA	64 100	NA NA
Seabold et al, 1984 ²⁰	3/128	74	100	100	99
Segall and McDougall, 1986 ⁵	68/155‡ 11/155§	92 38	66 99	35 91	98 89
NA = not available	23/155†	35	89	39	87

*Only positive scans were examined.

†Focal uptake.

‡All grades.

§Grade III or IV.

be ascertained, but our experience suggests that the chest uptake of this radioisotope in the context of occult infection warrants further diagnostic surveillance for the possibility of pneumonia.

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